

The University of Chicago

**UREA DERIVATIVES OF SOME IMINO
COMPOUNDS**

**A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY**

DEPARTMENT OF CHEMISTRY

1936

By

JULIA LURENA SOUTHARD

**Private Edition, Distributed by
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UREA DERIVATIVES OF SOME IMINO COMPOUNDS

The great similarities in the chemical behavior of malonic and aceto-acetic esters suggested that ureides of dialkyl aceto-acetic acid might be found to have certain hypnotic effects comparable to those of hypnotics of the barbituric acid series. In particular the analogue of phenobarbital (luminal),¹ a valuable drug used in epilepsy but rather toxic, was aimed at in the hope that it would be less toxic than phenobarbital itself. The preparation of such dialkylacetoacetic acid ureides, 4-methyl-5, 5-dialkyl uracils, $\text{HN.CO.N:C(CH}_3\text{).C(R}_1\text{R}_2\text{)CO}$ met with great and unexpected difficulties, as a result of which the methods of attack on the synthetic problem were broadened. One later line of approach was an investigation of urea derivatives obtained from such imino compounds as result from the condensations of nitriles by the aceto-acetic ester type of condensation. E. von Meyer² and his collaborators condensed acetonitrile to form β -imino aceto-acetic nitrile, $\text{H}_3\text{C.C(:NH)CH}_2\text{CN}$. Alkylation of the $-\text{CH}_2-$ group by methods analogous to those used for the alkylation of aceto-acetic ester itself were well known.³

On the other hand, very little was known about the conversion of ketimines into ureas and about the conditions under which such ureas could be obtained. The present paper deals in particular with this phase of the general problem.

¹Rising and Stieglitz, J. Am. Chem. Soc., **40**, 725 (1918).

²von Meyer, J. pr. Chem., **52**, 81 (1895); Warnecke, Ph.D. Dissertation, University of Heidelberg (1902).

³Ibid.

In the first part of this study an attempt was made to prepare ethyl α -phenyl- α -ethyl- β -phenyl- β -ureido butyrate, $C_6H_5C(:HCONH_2)C(C_6H_5)(C_2H_5)CO_2C_2H_5$. Benzyl cyanide was used as the initial compound. It was ethylated by the use of sodium amide and ethyl bromide as described by Bodroux and Taboury.¹ The resulting α -phenyl butyronitrile was converted to α -phenyl butyric acid through the imino ester by application of the general method of Pinner.² A bromine atom was introduced into the α -position and the ethyl ester of the acid prepared. The ethyl ester was stable enough to purify³ by distillation under reduced pressure.

The pure ethyl α -phenyl- α -bromo butyrate, $C_6H_5C(C_2H_5)BrCO_2C_2H_5$ was then treated with magnesium in ether to form a Grignard derivative; this was to be added to benzo nitrile⁴ to prepare β -phenyl- β -imino- α -phenyl- α -ethyl butyric acid ethyl ester, $C_6H_5C(:NH)C(C_6H_5)(C_2H_5)COOC_2H_5$, if possible, by condensing the β -imino ester with cyanic acid or potassium isocyanate. If once the ureide were formed, the problem of closing the ring might be accomplished with relative ease.

However, neither the free β -imino ester nor the ureide could be isolated from the crude condensation product with the Grignard reagent. Because of the limited knowledge of the general behavior of the imino groups in forming ureides, other than their sensitivity to hydrolysis, it was decided at this point to study the condensation of simple imino compounds with cyanic acid and

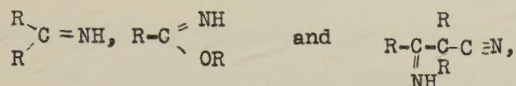
¹Bull. Soc. Chem., ser. 7, 4, 666-667 (1910).

²Pinner, "Die Imidoäther und ihre Derivative," R. Oppenheim, 1892, p. 303.

³Lackey, Master's Dissertation, University of Chicago (1927); Ray, Ph.D. Dissertation, University of Chicago (1925).

⁴Moureu and Mignanac, Compt. rend., 156, 1801-06 (1913); Ann. Chim., ser. 9, 14, 322-59 (1920).

phenyl isocyanate. The knowledge thus gained was to be applied in time to the preparation of the more complex ureides of special interest to us. Imino compounds represented by the following general formulae,



were used for this part of the study. The condensation product of phenyl isocyanate with the imino compound, in each instance, proved to be the expected phenylureido¹ derivative.

Efforts to produce a non-phenylated ureide by the use of free cyanic acid did not meet with the same success. Diphenyl ketimine formed a biuret derivative; methyl imino benzoate gave only a condensation product of itself; but the α, α -diethyl β -imino butyronitrile gave a fair yield of the ureide.

This product should prove to be an important stepping stone toward the final synthesis of the 5,5 dialkylated uracils which has proved so difficult of attainment.

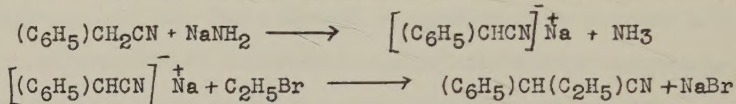
¹Smith and Bergstrom, J. Am. Chem. Soc., 56, 2095 (1934).
(This work was reported after the experimental work had been done for the present paper.)

EXPERIMENTAL PART

I. Attempt to Prepare 4-Phenyl-5-Ethyl-5-Phenyl Uracil, $\text{HNCON:C(C}_6\text{H}_5\text{):C(C}_6\text{H}_5\text{)(C}_2\text{H}_5\text{)CO}$

Preparation of α -phenyl butyronitrile, $\text{C}_6\text{H}_5\text{CH(C}_2\text{H}_5\text{)CN}$.

This compound was prepared according to the Rising and Lackey¹ modifications of the method of Bodroux and Taboury.² Sodium amide acted upon benzyl cyanide to form the sodium salt which in turn reacted with ethyl bromide to give α -phenyl butyronitrile, as represented by the following equations of Rising and Lackey:³



A three-necked, round bottomed flask was fitted with a stirring device and mercury seal, a dropping funnel, and a Liebig condenser protected with a charged calcium chloride tube. The system was dried by gentle warming over a hot plate in a current of dry air. Sodium amide (44g.) was finely ground in a well dried mortar and quickly⁴ transferred to the dried flask to which had been added approximately 200 grams of anhydrous ether. Freshly distilled benzyl cyanide (120 g.) was dissolved in a 200 gram portion of dry ether. Over a period of about six hours this solution was added dropwise to the above mixture which was stirred constantly. After the cyanide had been added, the mixture was

¹Lackey, Master's Dissertation, University of Chicago (1927).

²Bull. Soc. Chim., ser. 7, 4, 666-667 (1910).

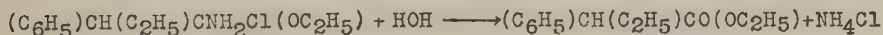
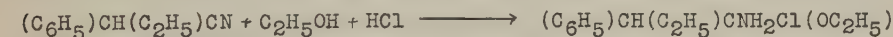
³Lackey, *op. cit.*

⁴Sodium amide reacts rapidly with moisture in the air.

refluxed for two hours on a water bath in order to complete the formation of the sodium salt of the cyanide. Freshly distilled ethyl bromide (106 g.) was then introduced dropwise with constant stirring over a period of about six hours. After that the mixture was again refluxed for two hours, and finally allowed to stand overnight. The next day the unused sodium amide was decomposed by the careful addition of water to the reaction mixture. The mixture was transferred to a separatory funnel in order to separate the ether layer from the aqueous layer. The latter was extracted three times with 50 cc. portions of ether. The ether extracts were combined with the main ether solution and dried over anhydrous calcium chloride. The ether was removed from the product by evaporation over the water pump and the oil which remained was distilled at 141-2° at 41 mm. The boiling point as extrapolated from a curve given by Zee¹ is 140.5° at 41 mm. The yield was 92 per cent of the theoretical.

Preparation of α -phenyl butyric acid, $C_6H_5CH(C_2H_5)CO_2H$.

The general method of Pinner² for the preparation of imino esters was followed. A continuous process as elaborated by Rising and Lackey³ and represented by the following equations was used to convert α -phenyl butyronitrile into α -phenyl butyric acid.



One volume of α -phenyl butyronitrile was added to approximately two volumes of absolute ethanol in a dry filter

¹T.W. Zee, Ph.D. Dissertation, University of Chicago (1927).

²Pinner, loc. cit.

³Lackey, loc. cit.

flask. A rapid current of dry hydrogen chloride was passed through the mixture, maintained at -10° , until saturation was complete. The mixture was allowed to stand overnight in a refrigerator. White needle-like crystals of the imino ester salt were present. As much as possible of the excess of hydrogen chloride and ethanol was removed under reduced pressure on a water bath. The crude mixture was then shaken with a solution of equal volumes of 95 per cent ethanol and water, and heated until the oily layer of ethyl

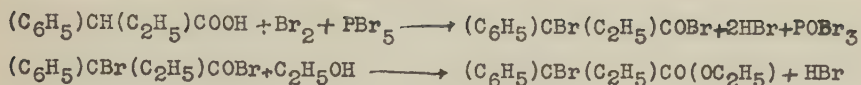
α -phenyl butyrate separated. The aqueous portion was extracted with ether. The ether extract was washed with half its volume of a cold saturated sodium chloride solution. The ether was evaporated from the product and the combined oil fractions were added to 20 per cent potassium hydroxide solution and gently refluxed. The mixture was extracted with ether in order to remove any unchanged nitrile, then the aqueous portion was acidified by the addition of hydrochloric acid. The α -phenyl butyric acid was extracted with ether, and the ether extract dried over anhydrous sodium sulfate. The ether was evaporated and the oil distilled at $178-9^{\circ}$ at 41 mm. When cooled in an acetone-carbon dioxide bath, this oil became a white crystalline mass which melted at $41-43^{\circ}$. The recorded melting point of α -phenyl butyric acid is 42.5° .¹ The yield of acid was 66 per cent of the calculated.

Preparation of ethyl α -phenyl α -bromo butyrate,
 $C_6H_5CBr(C_2H_5)CO_2C_2H_5$.- α -phenyl butyric acid was converted into the ester of α -phenyl α -bromo butyric acid by preparation of the acid bromide of the α -bromo acid and treatment of the acid bromide with alcohol. The sequence of reactions used by Rising and Lackey² was followed but a modified experimental

¹Ibid.

²Ibid.

procedure was adopted.

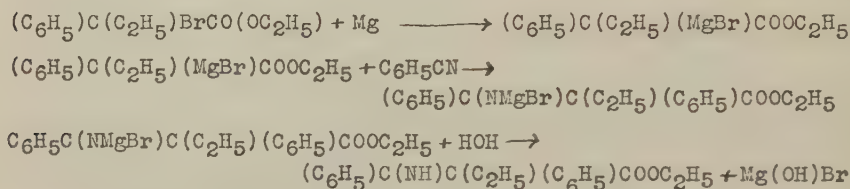


The acid was mixed in a 500 cc. round bottomed flask with red phosphorus and solid glass beads, and the mixture was well shaken in order to distribute the acid and phosphorus over the surface of the beads. Dry bromine (45 g.) was placed in a dropping funnel with a capillary directly above the flask. The latter was illuminated with two 60 watt lamps, one placed on each side. About two-thirds of the bromine was introduced over a period of three hours. The reaction was vigorous. The flask and contents were thoroughly shaken every few minutes in order to insure uniformity of the mixture. After the addition had been completed, the reaction mixture was allowed to stand for one hour on a steam bath. Then the remaining one-third of the bromine was added more rapidly. The flask was stoppered and the contents allowed to remain overnight at room temperature. The next morning the red oil, α -phenyl- α -bromo-butyryl bromide, was converted into the ester by being dropped slowly into absolute ethanol which was chilled in an ice bath. After all the bromide had been added, the flask containing the mixture was gently heated on a steam bath for one and one-half hours to remove as much as possible of the hydrogen bromide and the excess of ethanol. The crude

α -phenyl- α -bromo-butyric ethyl ester was taken up in ether and the extract washed with a 3 per cent solution of sodium bicarbonate until no longer acid to litmus. The water pump was used to aid in the removal of the ether and in rapid drying. The oil was placed to dry at 6 mm. pressure in a vacuum desiccator containing phosphorus pentoxide and concentrated sulfuric acid. When the red brown oil was dry, it was stable enough to be

purified by distillation at 2 mm. The fraction which distilled at 135-142° at 2 mm. gave 29.05 per cent bromine by the Drogin-Rosanoff method.¹ The calculated per cent of bromine is 29.50. The pure ester was a pale yellow oil. There were no fumes apparent from decomposition. The yield of pure ester was approximately 50 per cent of the calculated amount.

Attempted preparation of ethyl α -phenyl- α -ethyl- β -phenyl- β -imino propionate, $(C_6H_5)C(:NH)C(C_2H_5)(C_6H_5)CO_2C_2H_5$. The following equations represent the steps by which it was hoped to prepare ethyl α -phenyl- α -ethyl- β -phenyl- β -imino propionate:



The preparation of the ketimines by the addition of a suitable Grignard reagent to a nitrile was first carried out by Moureu and Mignonac,² and their procedure was in general followed. The apparatus for this reaction was set up and dried as previously described (page 1). Dry granulated magnesium (0.4 g. Kahlbaum) together with a crystal of iodine was placed in a reaction flask, and the latter was warmed until it was full of purple vapors from the iodine. After the flask had cooled, 100 cc. of anhydrous ether was introduced and an ethereal solution of ethyl α -phenyl- α -bromo butyrate (4 g.) was slowly added to it through the dropping funnel. Heat was generated slowly at first, but soon the ether boiled vigorously. The reaction soon slowed down and the flask

¹Drogin and Rosanoff, J. Am. Chem. Soc., **38**, 711 (1916).

²Moureu and Mignonac, loc. cit.

was heated on a water bath for an hour. The reaction mixture was greyish-green in color. When there seemed to be no further reaction, benzonitrile (1.5 g.) in ether solution was added rapidly to the mixture through the dropping funnel. The addition of the nitrile caused a whitish precipitate to form and a dark oil to settle to the bottom of the flask. After the nitrile had been added, the flask was heated for three hours on a water bath, and then allowed to stand overnight.

The Grignard product was decomposed by a saturated solution of ammonium chloride¹ at -15° , made from ammonium chloride and crushed ice. A heavy white precipitate formed as soon as the solution was added. The mixture was extracted with ether as quickly as possible. Ammonia was rapidly evolved from both the ether extract and the aqueous portion. The ether extract was shaken with one portion of anhydrous sodium sulfate; placed over a second portion, and allowed to stand overnight in the refrigerator. The ether was evaporated in a desiccator under reduced pressure. At $127-134^{\circ}$ and 14 mm. it was possible to distill without apparent decomposition only one or two cc. of a reddish-brown oil. This oil quickly became brown in the air.

It was then thought best to try to isolate a derivative of the ketimine in the form of the ureide. An ether solution of the ketimine was treated directly with cyanic acid. For this purpose the Grignard reaction was repeated according to the above procedure, and part of the ether solution of the resulting product was pumped from the reaction flask into another dry flask. Care was used to prevent the product from coming in contact with the air. The ether solution was cooled to -10° in an ice and salt bath. The cyanic acid was carried into it by means of a current of dry

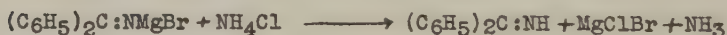
¹Culbertson, Ph.D. Dissertation, University of Chicago (1927).

carbon dioxide. The cyanic acid, which was generated by heating cyanuric acid, was bubbled through the solution for one and one-half hours. A reddish-brown oily layer settled out, but it was not possible to isolate a ureide from it.

Due to the failure to obtain the ketimine either as such or in the form of its ureide, no further progress was made toward the preparation of the desired 4-phenyl-5-ethyl-5-phenyl uracil. It seemed advisable at this point to study the behavior of more simple imino compounds toward phenyl isocyanate and cyanic acid, respectively. For this purpose it was decided to use diphenyl ketimine, methyl imino benzoate, and α , α -diethyl- β -imino butyronitril. The latter compound was very similar to ethyl α -ethyl- α -phenyl- β -imino- β -phenyl propionate, the preparation of which had been attempted above.

II. Preparation of Phenyl Ureido Benzophenone, (C₆H₅)₂C:NCONH(C₆H₅)

Preparation of diphenyl ketimine, (C₆H₅)₂C:NH.- Diphenyl ketimine¹ was prepared by the action of phenyl magnesium bromide on benzonitrile according to the following equations:



A standard Grignard reaction flask was prepared as previously described. Dry granulated magnesium (12g. Kahlbaum), together with a crystal of iodine, was introduced at a side arm. The flask was warmed to vaporize the iodine, then cooled, and dry ether (450 cc.) introduced. Redistilled bromobenzene (125g.) was slowly dropped into the flask. After an initial lag, cooling was necessary in order to prevent the reaction from proceeding

¹Moureu and Mignonac, Compt. rend., 156, 1801 (1913).

too rapidly. After all of the bromobenzene had been added, the mixture was allowed to stand for one hour before the benzonitrile was introduced. An ethereal solution of benzonitrile was slowly run in through the dropping funnel. The introduction of the nitrile caused the ether to reflux again, but more slowly. The reaction mixture remained quite black until almost all of the nitrile was in, then it became a solid mass of greenish-grey material. After the mixture had stood overnight, the condensation product was decomposed at -15° with a saturated aqueous solution of ammonium chloride.¹ The mixture was shaken in order that the ketimine would be taken up by the ether as rapidly as it was liberated from its magnesium salt. The ether extract was separated from the aqueous layer, shaken with two separate portions of anhydrous sodium sulfate, and set aside to dry over a third portion in a desiccator containing phosphorus pentoxide and concentrated sulfuric acid. The ether extract was later decanted, and the sodium sulfate shaken twice with fresh portions of dry ether to remove most of the adhering ketimine. After the ether had been evaporated, the pale yellow residue was distilled at $160-163^{\circ}$ under 1.5 mm. The recorded boiling point is 168° at 14 mm.² The yield was excellent.

Preparation of phenylureido benzophenone,³ $(C_6H_5)_2C:NCONHC_6H_5$.- Diphenyl ketimine condensed with phenyl isocyanate to yield phenylureido benzophenone according to the following equation:



A calculated amount of phenyl isocyanate was added to diphenyl

¹Culbertson, op. cit.

²Breckpot, Unpublished work, University of Chicago (1925).

³This compound has since been reported by Smith and Bergstrom, op. cit.

ketimine. The weighing bottle holding this mixture was placed in a beaker of water at 60° and allowed to remain for 1.5 hours. Crystals started forming at once and much heat was evolved. Soon the brownish-yellow reaction mixture became a solid mass which had to be cut out of the container. Recrystallization of the crude phenylureido benzophenone from dry benzene (toluene or ether may also be used) gave pale yellow needle-like crystals. After a third recrystallization and careful drying, the crystals melted at 158-160°. Analyses for nitrogen gave the following results:¹

Substance, 5.000 mg gave 9.43% N

6.265 mg gave 9.17% N

Calculated for $C_{20}H_{16}ON_2$ 9.33% N

A 1.3 N solution of hydrochloric acid was added to some of the product, phenylureido benzophenone, and the mixture was warmed. The crystals went into solution at once and an oil appeared. The oil was extracted with ether. After evaporation of the solvent, the residue was converted into the oxime. The latter, without recrystallization, melted at 139-141° (benzophenone oxime, m.p. 141-2°). The oil was thus identified as benzophenone. The original solution, from which the benzophenone had been obtained, gave on cooling, silky plates, which, after recrystallation from water, melted at 146-147.5°. This product was monophenyl urea (m.p. 146-7°).

A calculated amount of phenyl isocyanate was added to another portion of diphenyl ketimine and kept at room temperature. Much heat was evolved at first. The reaction mixture formed a brownish-yellow solid mass slightly less rapidly than in the preceding case, wherein it was held at 60°. Although there

¹Micro-analyses were used in all of this work and are according to Pregl unless otherwise stated.

seemed to be no further change in appearance after the first few minutes, the reaction mixture was allowed to stand for two days. The crystals were placed in hot benzene for recrystallization. A few large yellow ones did not dissolve even on further addition of benzene. They were identified as carbanilide. Evidently some moisture had reacted with phenyl isocyanate to give symmetrical diphenyl urea, which upon recrystallization melted at 235-236°. Nitrogen analyses were as follows:

Substance: 2.710 mg, 13.25% N

Calculated for $C_{13}H_{12}ON_2$ 13.21% N

Calculated for $C_{20}H_{16}ON_2$ 9.33% N

Thus, the crystals which had dissolved in the hot benzene proved to be phenylureido benzophenone. This compound was identical with that secured by holding the reaction mixture at 60° for one and one-half hours. The pale greenish-yellow needles melted at 158-160°, and gave, on hydrolysis with a 1.3 N solution of hydrochloric acid, monophenyl urea and benzophenone.

III. Preparation of Methyl Phenylureido Benzoate, $C_6H_5(:NCONHC_6H_5)(OCH_3)$

Preparation of methyl imino benzoate, $C_6H_5(:NH)(OCH_3)$.-

Methyl imino benzoate was prepared according to the general method of Pinner.¹ Dry hydrogen chloride was passed into a solution of dry benzonitrile (80 g.) in absolute methanol (32 g.) at -10° until the mixture was practically solid with shining white crystals. The flask and contents, protected from moisture with a calcium chloride tube, were placed in the refrigerator overnight. Next morning the flask was set in warm water and evacuated with the water pump for several hours. After removing as much as possible of the excess of hydrogen chloride, and after chilling the flask with a mixture

¹Pinner, op. cit.

of crushed ice and ammonium chloride, three times the calculated amount of 30 per cent sodium hydroxide (cooled to 0°) was cautiously added with stirring to liberate the methyl imino benzoate from its hydrochloride. Ether, previously added, took up the free methyl imino benzoate as rapidly as it was set free. Granular anhydrous calcium chloride was added to the ether extract and it was set in the refrigerator. Two days later the ether extract was decanted from the calcium chloride, the ether evaporated on the steam bath, and the ester distilled. The product came over between 85 and 87.5° at 2 mm. The recorded boiling point is 75.5° at 3.8 mm.¹ Little residue was left in the flask. The yield was low, 35% of that calculated.

Preparation of methyl phenylureido benzoate, $C_6H_5C(:NCO)NHC_6H_5(OCH_3)$. Methyl imino benzoate condensed with phenyl isocyanate to give methyl phenylureido benzoate according to the following equation:



A calculated amount of phenyl isocyanate was added to the pure methyl imino es'. Much heat was evolved. The mixture first became a clear thick syrup, and within five minutes had changed to a solid white mass of crystals. The crystals which were very soluble in benzene, were easily purified by crystallization from that solvent. They were silky snow white flakes which melted at 110-112°. Analyses for nitrogen gave the following results:

Substance: 5.016 mg gave 11.56% N

5.381 mg gave 11.13% N

Calculation for $C_{15}H_{14}O_2N_2$ 11.02% N

Some of the crystals which melted at 110-112° were added

¹Ira H. Derby, Ph.D. Dissertation, University of Chicago (1908).

to 1.5 N hydrochloric acid. On warming there seemed to be no evidence of a reaction except the appearance of a very pleasant ethereal odor (probably that of methyl chloride) which practically disappeared upon boiling. That portion which remained a solid was collected on a filter and recrystallized from absolute ethanol. It was identified as benzoyl phenylurea ($C_6H_5CONHCOHNC_6H_5$) by its melting point (206-208°) and by analysis.

Nitrogen analyses gave the following results:

Substance: 8.195 mg gave 11.33% N

1.680 mg gave 11.64% N

Calculated for $C_{14}H_{12}O_2N_2$ 11.62% N

The formation of benzoyl phenylurea by the action of hydrogen chloride on the methyl phenylureido benzoate occurs according to the equations:



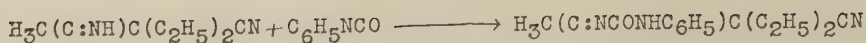
The filtrate was partly evaporated and cooled, but no further precipitate appeared.

Part of the original condensation product, methyl phenylureido benzoate, slowly dissolved in 10 per cent potassium hydroxide solution. When the solution was chilled in an ice bath, a flaky precipitate appeared. It was identified by its melting point of 145-146° as monophenylurea.

IV. Preparation of α, α -Diethyl- β -Phenylureido Butyronitrile, $H_3C(C:NCONHC_6H_5)C(C_2H_5)_2CN$

Pure dry α, α -diethyl- β -imino butyronitrile¹ was treated with phenyl isocyanate with the object of forming α, α -diethyl- β -phenylureido butyronitrile as expressed by the equation:

¹Lowe, Unpublished work, University of Chicago.



The reaction was carried out under three different sets of conditions. First, phenyl isocyanate was added to a weighed amount of the pure nitrile and the mass became very slightly warm. The container holding this mixture was placed in an oil bath at 152° for one hour, and then allowed to cool slowly. On heating, the mixture became dark red and very viscous. The product was hard and brittle when it was cold. When crushed, the crude material was a yellow powder, a part of which was soluble in dry chloroform. By adding ligroin (b.p. 30-35°) to the chloroform solution, it was possible to get some fine white needles which became tan at 180°, shrank sharply at 220°, and became a brown liquid at 230°. This product could be purified until it gave a m. p. of 238-240°. It was difficult to start crystallization until the product was relatively pure. The compound was most easily purified by recrystallization from hot absolute ethanol.

Besides the desired ureide the composition of which is $\text{C}_{15}\text{H}_{19}\text{ON}_3$, the presence of carbanilide, $(\text{C}_{13}\text{H}_{12}\text{ON}_2)$, was suspected as a product of the action of water on phenyl isocyanate.

Nitrogen analyses were as follows:

Substance: 4.551 mg. gave 15.37% N

4.642 mg. gave 15.16% N

Theoretical for $\text{C}_{15}\text{H}_{19}\text{ON}_3$ 16.33% N

Theoretical for $\text{C}_{13}\text{H}_{12}\text{ON}_2$ 13.21% N

The yield was so very low, that it was decided to determine molecular weights on the remaining material rather than ascertain the nature of the hydrolysis products. Micro-molecular weights were determined in camphor.¹

¹Rast, Ber., 55, 1051, 3727 (1922).

Substance: 0.0233 mg. gave 256.3 g. mol. wt.

0.0223 mg. gave 245.7 g. mol. wt.

0.2428 mg. gave 260.9 g. mol. wt.

Theoretical for $C_{15}H_{19}ON_3$ (α, α -diethyl- β -phenylureido butyronitrile) is 257.2 g. mol. wt.

Theoretical for $C_{13}H_{12}ON_2$ (carbanilide) is 212.0 g. mol. wt.

Further evidence that the product was not carbanilide, ($C_{13}H_{12}ON_2$), was indicated by the melting point of the mixture of known carbanilide with the product.

<u>Compound</u>	<u>M.P.</u>
Carbanilide	235°
Mixture of carbanilide with the product	194-230°
The product	238-240°

A second attempt was made to secure the ureide in better yields. Phenyl isocyanate was added in slight excess to another portion of the imino nitrile (4 g.). This mixture was allowed to remain at room temperature. At the end of twelve days a few needle-like crystals began to form. The white crystals melted at 189-190° after several recrystallizations from absolute ethanol.

Nitrogen analyses were as follows:

Substance (m.p. 186-188°)	2.020 mg. gave 15.26% N
	2.411 mg. gave 15.34% N
(m.p. 189-190°)	2.214 mg. gave 16.50% N

Theoretical for $C_{15}H_{19}ON_3$ (α, α -diethyl β -phenylureido butyronitrile) is 16.33% N.

Finally, since it had been possible to secure only very low yields in the two previous instances, it was decided to repeat the reaction in a solvent. A slight excess of phenyl isocyanate was added to the nitrile (5 g.) in dry toluene; the mass became quite hot. The flask containing this mixture was

stoppered and set away in a desiccator at room temperature for five days. The reaction mixture was then poured into a crystallizing dish, the flask rinsed with absolute ethanol, and the mixture set in an acetone-carbon dioxide bath to chill. Ligroin (200 cc. of b.p. 30-35°) was added, and the mixture stirred. A gummy mass collected on the bottom of the dish. The ligroin was decanted and both the ligroin and the gummy mixture were placed in a desiccator until morning. The gummy mass was dissolved in a few cubic centimeters of absolute ethanol and again chilled in an acetone-carbon dioxide bath. Ligroin (250 cc. of b.p. 30-35°) was again used to bring about precipitation of the compound. Fine white needle-like crystals resulted. These were collected on a filter and recrystallized. The compound decomposed at 133-135° but was not identified as analyses on the product which melted at 195° (190°) showed the latter to be the desired phenyl ureide. However, the analyses which were made on the compound (m.p. 133-135°) are described below. When the product was heated in 1 N hydrochloric acid, it yielded an oily material which, upon recrystallization from benzene, decomposed at 177-179°. Nitrogen analyses were as follows:

Substance: 1.303 mg. gave 18.74% N

1.435 mg. gave 18.60% N

Theoretical for $C_9H_{10}O_2N_2$ (acetyl phenyl urea) is 15.73% N.

Melting point of a mixture follows:

Substance (m.p. 177-179°) 178°

Mixture of substance and acetyl phenyl urea 140-155°

Acetyl phenyl urea 183°

Thus both nitrogen analyses and melting points indicated that the compound (m.p. 177-179°) was not acetyl phenyl urea.

Another portion of the product (m.p. 133-135°) was warmed

in 10 per cent potassium hydroxide. The filtrate yielded silky-white needles which decomposed to a brown liquid at 235-238°.

Nitrogen analyses¹ on this product were as follows:

Substance: 0.846 mg. gave 15.55% N

1.080 mg. gave 15.57% N

Theoretical for $C_{13}H_{12}ON_2$ (carbanilide) is 13.21% N.

Theoretical for $C_{15}H_{19}ON_3$ (α, α -diethyl β -phenyl-ureido butyronitrile) is 16.33% N.

Melting points of mixtures follow:

- (1) Substance (m.p. 235-238°) 235-238° brown liquid
Mixture of substance (m.p. 235-238°) and carbanilide 166-223° brown liquid
Carbanilide 235-237° clear liquid
- (2) Substance (m.p. 235-238°) 235-238° brown liquid
Mixture of substance of (m.p. 235°) and substance of (m.p. 194-195°) . . . 105-180° brown liquid
Substance melting (m.p. 194-195°) . 194-195° clear liquid
- (3) Substance (m.p. 235-238° d) 235° brown liquid
Mixture of substance (m.p. 235°) and substance (m.p. 220°) 189-194° brown liquid
Substance (m.p. 220-222°) 218-220° clear liquid

Neither the original substance (m.p. 133-135°) nor the hydrolysis products (acid or alkaline) were identified.

The combined ligroin fractions from the precipitation of the compound (m. p. 133-135°) were evaporated to approximately 50 cc. over a hot plate and the mixture was chilled in an acetone-carbon dioxide bath. This time when ligroin was added, a fine granular precipitate resulted. This product was purified by recrystallization from absolute ethanol. It gave rosette-like clusters of crystals which decomposed at 195°. The product was

¹Compare melting point and nitrogen analyses with those obtained on the product secured by heating the reaction mixture to 152°.

found to be the desired α, α -diethyl- β -phenylureido butyronitrile. Nitrogen determinations gave the following results:

Substance: 5.191 mg. gave 16.13% N
3.714 mg. gave 15.95% N

Theoretical for $C_{15}H_{19}ON_3$ (α, α -diethyl- β -phenylureido butyronitrile) is 16.33% N.

A portion of the substance was boiled with 1 N. hydrochloric acid. It did not seem to go into solution but seemed to change its appearance. The solid material was collected on a filter, purified by recrystallization from dry benzene, and analyzed. It decomposed at 220-222° and was found to be another form of the original α, α -diethyl- β -phenylureido butyronitrile. Nitrogen analyses gave the following:

Substance: 3.015 mg. gave 15.68% N
2.113 mg. gave 16.09% N

Theoretical for $C_{15}H_{19}ON_3$ (α, α -diethyl- β -phenylureido butyronitrile) is 16.33% N.

Melting points gave the following results:

Substance which decomposed at 195°	195°
Mixture of substances melting at 195° and 220°	220-222°
Substance which decomposed at 220-222°	220-222°

Another portion of the substance which decomposed at 195° dissolved when warmed with 10 per cent solution of potassium hydroxide. The aqueous portion was neutralized with dilute hydrochloric acid. Phenylurea slowly crystallized out. Melting points are as follows:

Material from the alkaline hydrolysis liquified	143°
Mixture of hydrolysis product with known phenylurea	144°
Known phenylurea	146°

The experiment confirms the structure assigned to the ureide on

the basis of its synthesis.

V. Attempt to Prepare Ureido Benzophenone,
 $(C_6H_5)(C_6H_5)C:NCONH_2$

Benzophenone biuret, $(C_6H_5)_2C:NCONHCONH_2$.- Diphenyl ketimine was treated with cyanic acid with the purpose of preparing ureido benzophenone according to the following equation:



The first attempt to secure a condensation product of cyanic acid with diphenyl ketimine (4 g.) was by saturating a chloroform solution of the ketimine (at -10°) with cyanic acid vapors. A 33 per cent solution (5 cc.) of trimethylamine in ethanol was added to the mixture with the purpose of preventing the formation of polymers of cyanic acid. A compound was isolated which melted upon recrystallization from ethanol at $191-192^\circ$ and was identified as allophanic ethyl ester¹ which had been formed according to the following equation:



Analyses for the elements were as follows:

Substance:	1.782 mg. gave	20.86% N	
	2.002 mg. gave	20.33% N	
	2.522 mg. gave	7.56% H;	35.21% C
	1.547 mg. gave	10.00% H;	35.22% C

Theoretical for $C_4H_8O_3N_2$ (allophanic ethyl ester)
 21.21% N
 6.10% H; 36.35% C.

Molecular weights gave the following results:

Substance:	2.428 mg. gave	136.5 g. mol. wt.
	1.444 mg. gave	134.8 g. mol. wt.

Theoretical for $C_4H_8O_3N_2$ (allophanic ethyl ester)
 132.1 g. mol. wt.

A small amount of the material was heated in a dry test tube. At the mouth of the tube was a moist pink litmus paper which

¹W. Traube, Ber., 22, 1572 (1889).

became blue; a white residue of cyanuric acid was deposited on the cooler portions of the tube.

When the second attempt to secure the ureide was made, the same experimental procedure was followed, except that no trimethyl amine was used. A white crystalline product was isolated from the chloroform solution and after several recrystallizations from absolute ethanol, it melted at 172-175° where it again became a white solid. The composition of the compound showed that in forming, two molecules of cyanic acid had combined with one molecule of the ketimine. There are three possible methods of combination which would leave the radical $(C_6H_5)_2C<$ intact in the product:

(a) A biuret derivative is formed:



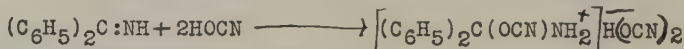
Its formation would correspond to the production of allophanic ester in the earlier experiment. Benzophenone (see below) was fully identified as a product of hydrolysis of the compound, but unfortunately the material was exhausted before a proper biuret test could be made.¹

(b) A salt of two molecules of cyanic acid and one of the ketimine is formed:



This structure is barred by the comparative stability of the compound. There is no evidence of immediate decomposition by acid.

(c) A cyanate of an addition product is formed:²



¹Mr. Ma will prepare the compound and attempt to confirm the presence of the biuret group.

²This would correspond to the observation of Bergstrom and Smith, J. Am. Chem. Soc., 54, 2095 (1934), on the action of hydrocyanic acid.

This structure is to be eliminated on the same grounds as (b).

Consequently the compound melting at 172-175° must be considered to be benzophenone biuret.

Nitrogen analyses were as follows:

Substance: 3.932 mg. gave 15.75% N

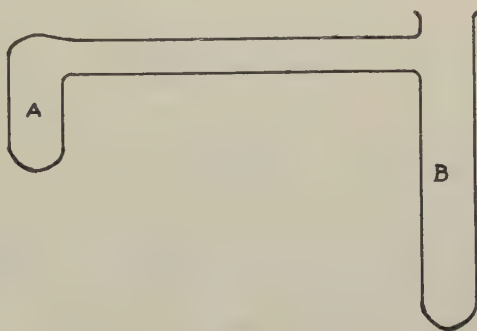
4.010 mg. gave 15.70% N

Theoretical for $C_{14}H_{12}ON_2$ (ureido benzophenone) is 12.49%N

Theoretical for $C_{15}H_{13}O_2N_3$ (benzophenone biuret) is 15.73% N.

The yield was low, as it was decided to repeat the reaction under different conditions, using larger quantities of materials.

The accompanying figure shows the type of reaction flask used. Cyanuric acid was placed in arm A. Arm B was placed in a



Dewar containing ethanol and carbon dioxide. Arm A was heated with a free flame and the cyanic acid which resulted from the decomposition of cyanuric acid distilled over into arm B where it was condensed. The ketimine (10 g.) was dropped into the liquid acid through the dropping funnel. There was a mildly explosive reaction in which most of the cyanic acid seemed to be converted into a polymer. A small amount of white crystalline material was isolated from the benzene soluble portion of the reaction mixture.

The material melted from 172-175° where it became a white solid. Two molecules of the acid combined with one molecule of the base and gave not the expected ureido benzophenone but a compound which seemed to be a biuret derivative of the ketimine, $(C_6H_5)_2C:NCONHCO NH_2$. Nitrogen analyses gave the following results:

Substance: 1.316 mg. gave 15.72% N

1.165 mg. gave 16.28% N

Theoretical for $C_{14}H_{12}ON_2$ (ureido benzophenone) is 12.49% N

Theoretical for $C_{15}H_{13}O_2N_3$ (benzophenone biuret) is 15.73% N

These analyses checked those made previously on the product obtained in the second attempt to secure the ketimine.

The products from the last two preparations which melted at 172-175°, on hydrolysis with 1 N hydrochloric acid, gave benzophenone as proved by the oxime which melted at 140-141°. In neither hydrolysis was it possible to secure urea and exhaustion of material prevented an adequate test for the biuret.

VI. Attempt to Prepare Methyl Ureido Benzoate, $C_6H_5C(:NCONH_2)(OCH_3)$

Methyl imino benzoate was treated with cyanic acid with the hope of preparing methyl ureido benzoate as represented by the following equation:



Methyl imino benzoate was placed in a flask containing a chloroform solution of trimethyl amine in ethanol. The flask with contents was kept at -10° while cyanic acid was carried by means of dry nitrogen gas into the solution of the imino ester for one hour. The nitrogen tank was connected with a glass tube which led almost to the bottom of a flask containing cyanuric acid. The side arm of the flask was, in turn, connected to a glass tube which carried the cyanic acid into the reaction flask which

contained the solution of the imino ester. The flask and contents were allowed to stand overnight in the ice box. Next day the precipitate was collected on a filter and dried. The crystals which were isolated were recrystallized from benzene. They melted at 230°C . The crystals proved to be cyanphenine, $\text{C}_{21}\text{H}_{15}\text{N}_3$, a polymer of benzonitrile.¹ Evidently the imino ester had lost the methyl alcohol added to it.

Nitrogen determinations gave the following results:

Substance: 2.120 mg. gave 14.22% N

1.461 mg. gave 14.22% N

1.326 mg. gave 14.09% N

The reaction was repeated and crystals were secured which melted at $234\text{--}235^{\circ}$ and gave on analysis the following values for nitrogen:

Substance: 2.425 mg. gave 13.02% N

2.374 mg. gave 13.11% N

Theoretical for $\text{C}_9\text{H}_{10}\text{O}_2\text{N}_2$ (methyl ureido benzoate) is 15.72% N.

Theoretical for $\text{C}_{21}\text{H}_{15}\text{N}_3$ (cyanphenine) is 13.59% N.

Micro-analyses for carbon and hydrogen gave the following results:

Substance: 3.427 mg. gave 5.67% H; 80.70% C

2.763 mg. gave 5.77% H; 80.36% C

Theoretical for $\text{C}_9\text{H}_{10}\text{O}_2\text{N}_2$ (methyl ureido benzoate) is 5.62% H; 61.18% C.

Theoretical for $\text{C}_{21}\text{H}_{15}\text{N}_3$ (cyanphenine) is 4.85% H; 81.55% C.

Melting points of mixtures gave the following results:

(1) Carbanilide $235\text{--}236^{\circ}$ clear liquid

¹Johnson and Wheeler, J. Am. Chem. Soc., 44, 1341-43 (1922); Pinner, Ber., 22, 1611 (1889).

Mixture of carbanilide and unknown -
softened at 200° and became a brown liquid at 214°

Unknown. 229-230° clear liquid

(2) Cyanphenine (prepared by another
method)¹. 231-233° clear liquid

Mixture of cyanphenine and unknown. 231-233° clear liquid

Unknown. 231-233° clear liquid

Molecular weights of the unidentified compound were determined in
camphor. There was some decomposition. However, the following
results were obtained:

Substance: 0.090 mg. gave 238.8 gm.

0.181 mg. gave 228.5 gm.

0.326 mg. gave 294.3 gm.

Theoretical for $C_9H_{10}O_2N_2$ (methyl ureido benzoate) is
178.0 gm.

Theoretical for $C_{21}H_{15}N_3$ (cyanphenine) is 309.0 gm.

The crystals seemed to be insoluble in .5 N hydrochloric
acid and the melting point was unchanged; they were soluble
neither in 10 per cent potassium hydroxide nor 25 per cent, even
on boiling.

Thus, the above analyses proved that the material isolated
was cyanphenine and not the desired product, methyl ureido benzoate.

VII. Preparation of α, α -Diethyl- β -Ureido Butyronitrile,
 $H_3C \cdot C(:NCONH_2)C(C_2H_5)_2CN$

Condensation of α, α -diethyl- β -ureido butyronitrile
with cyanic acid.- α, α -diethyl- β -imino butyronitrile was
treated with cyanic acid for the purpose of preparing α, α -
diethyl- β -ureido butyronitrile according to the following
equation:



¹Pinner, ibid.

The α, α -diethyl- β -imino butyronitrile was placed in an alcohol solution of trimethyl amine on an ice bath at -10° . The mixture had cyanic acid gas carried into it by nitrogen gas for one hour. A fine white granular precipitate resulted. The crude precipitate melted at $210-213^{\circ}$ leaving a residue. On recrystallization from absolute alcohol the crystals melted at 211° and decomposed (gas evolved) at 218° . This product was easily isolated and easily purified. Analyses for nitrogen gave the following results:

Substance: 4.522 mg. gave 23.05% N

3.353 mg. gave 23.18% N

Theoretical for $C_9H_{15}ON_3$ (α, α -diethyl- β -ureido butyronitrile) is 23.11% N.

A portion of the product was hydrolyzed by treatment with a 10 per cent potassium hydroxide solution. The crystals dissolved completely upon warming. The solution was then made slightly acid with hydrochloric acid. White crystals which were ultimately identified as acetyl urea appeared. On recrystallization they decomposed at $214-216^{\circ}$. This product of hydrolysis gave the following nitrogen determination:

Substance: 2.382 gm. gave 27.65%N

2.847 gm. gave 27.72%N

Theoretical for $C_3H_6O_2N_2$ (acetyl urea) is 27.44% N.

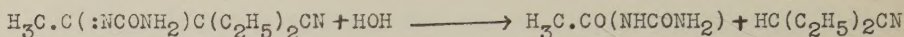
Theoretical for $C_9H_{15}ON_3$ (α, α -diethyl- β -ureido benzonitrile) is 23.11% N.

Melting points were taken on mixtures of the original and the hydrolysis product. The following were the results:

(a) Original compound $C_9H_{15}ON_3$ melted at 209°

(b) Original compound and hydrolysis product melted over wide range below 209° .

Acetyl urea would be the normal product of decomposition of α, α -diethyl- β -ureido butyronitrile, a compound of the 1,3 dicarboxyl type; cleavage occurs with aceto acetic ester between the alpha and the beta carbon atoms:



Summary

1. A magnesium derivative (Grignard) of α -phenyl- α -bromo butyric ethyl ester was allowed to act on benzonitrile but no β -imino benzoyl- α -phenyl butyric ester, $\text{C}_6\text{H}_5.\text{C}(:\text{NH})\text{C}(\text{C}_2\text{H}_5)(\text{C}_6\text{H}_5)\text{CO}_2\text{C}_2\text{H}_5$, was obtained.

2. Imino benzophenone produced with phenyl isocyanate phenylureido benzophenone; with cyanic acid benzophenone biuret, $(\text{C}_6\text{H}_5)_2\text{C}(:\text{N.CO.NH.CO.NH}_2)$, was formed instead of the simple urea derivative.

3. Methyl imino benzoate, $\text{C}_6\text{H}_5\text{C}(:\text{NH})\text{OCH}_3$, formed phenylureido methyl benzoate with phenyl isocyanate; when treated with cyanic acid the imino ester, under the conditions used, lost methyl alcohol and formed cyanphenine, the polymer of benzonitrile.

4. β -imino- α, α -diethyl aceto-acetic nitrile formed β -phenylureido- α, α -diethyl aceto-acetic nitrile when treated with phenyl isocyanate, and β -ureido- α, α -diethyl aceto-acetic nitrile, $\text{CH}_3\text{C}(:\text{NCONH}_2)\text{C}(\text{C}_2\text{H}_5)_2\text{C}\equiv\text{N}$, with cyanic ester.

